Consensus Recommendations for the Diagnosis and Treatment of Neuromyelitis Optica Spectrum Disorders (NMOSD): The MENACTRIMS Guidelines

Bassem Yamout[1], Riadh Gouider[2], Raed Al-Roughani[3], Salman Aljarallah[4], Nevine Shalaby[5], Jaber Al-Khabouri[6], Anu Jacob[7], Jihad Inshasi[8,9], Akram Mahdawi[10], Ahmed Shatila[11], Maya Zeineddine[12], Sarmad Al-Mashetah[10], Beatrice Canibano[13,14], Saeed Bohlega[15], Fatema Abdulla[16], Ilham Slassi[17], Aly Hassan[18], Sandra Ahmed[19], Magd Zakaria[20], Mohammed AlJumah[21], Yaser Al-Malik[22,23,24]

[1]*Neurology Institute, Harley Street Medical Centre, Abu Dhabi, United Arab Emirates*
[2]*Department of Neurology, LR18SP03, Clinical Investigation Center "Neurosciences and Mental Health"- Razi University Hospital- Mannouba, Tunis, Tunisia*
[3]*Amiri Hospital, Kuwait, Kuwait*
[4] *College of Medicine, King Saud University, Riyadh, Saudi Arabia*
[5]*Neurology Department, Cairo University, Kasr Al-Ainy School of Medicine, Cairo, Egypt*
[6]*Department of Neurology, The Royal Hospital, Muscat, Oman*
[7]*Neurology Institute, Cleveland Clinic Abu Dhabi, United Arab Emirates*
[8]*Neuroscience Department, Rashid Hospital, United Arab Emirates*
[9]*Dubai Medical College, United Arab Emirates*
[10]*Baghdad Teaching Hospital, Medical City Complex, Iraq*
[11]*Neurology Department Sheikh Shakhbout Medical City, Abu Dhabi, United Arab Emirates*
[12]*School of Pharmacy, Lebanese American University, Byblos, Lebanon*
[13]*Neuroscience Institute, Hamad Medical Corporation, Qatar*
[14]*Neuroscience Institute Weill-Cornell Medicine Qatar (WCMQ), Qatar*
[15]*King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia*
[16] *Salmaniya Medical Complex, Government Hospitals, Kingdom of Bahrain*
[17] *Hôpital Cheikh Khalifa Ibn Zaid, Casablanca, Morocco*
[18]*Department of Neurology, Tawam Hospital, Al-Ain, United Arab Emirates*
[19]*Department of Neurology, Multiple Sclerosis Clinic, Kasr Al-Ainy hospital, Cairo University*
[20]*Ain Shams University, Cairo, Egypt*
[21]*King Fahad Medical City, Ministry of Health, Riyadh, Saudi Arabia*
[22]*College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia*
[23]*King Abdullah International Medical Research Center, Riyadh, Saudi Arabia*
[24]*Department of Neurology, King Abdulaziz Medical City, National Guard Health Affairs, Riyadh, Saudi Arabia*

Corresponding Author:

Maya Zeineddine, PharmD, MSc, PhD

Clinical Associate Professor

School of Pharmacy, Lebanese American University, Byblos, Lebanon

Phone: +9613572654

Email: mzeineddine39@gmail.com; maya.zeineddine@lau.edu.lb

Key Points:

- This guideline provides region-specific recommendations to help doctors in the Middle East and North Africa diagnose and treat Neuromyelitis Optica Spectrum Disorder (NMOSD), a serious autoimmune disease often confused with multiple sclerosis.
- It highlights the importance of accurate antibody testing, early treatment of relapses, and use of approved therapies like monoclonal antibodies.
- The guidelines also address special cases such as children and pregnant women to improve patient outcomes across the region.

Running Head:

MENACTRIMS Consensus on NMOSD Diagnosis and Treatment in MENA

Abstract

Neuromyelitis Optica Spectrum Disorder (NMOSD) is a severe autoimmune disorder affecting the central nervous system, often misdiagnosed as multiple sclerosis. The identification of aquaporin-4–IgG (AQP4-IgG) has improved diagnostic precision and enabled targeted therapies. Given the unique regional challenges in healthcare delivery across the Middle East and North Africa (MENA) region, MENACTRIMS convened an expert panel to develop evidence-based, region-specific consensus recommendations for diagnosis and management.

These guidelines endorse the 2015 International Panel for NMO Diagnosis (IPND) criteria, emphasizing AQP4-IgG testing via cell-based assays. Differential diagnosis should consider multiple sclerosis, myelin oligodendrocyte glycoprotein antibody–associated disease (MOGAD), and acute disseminated encephalomyelitis (ADEM). For acute treatment, initiate high-dose intravenous methylprednisolone promptly; use plasma exchange early for severe or steroid-refractory attacks. For long-term immunotherapy, monoclonal antibodies (rituximab, inebilizumab, eculizumab, ravulizumab, satralizumab, or tocilizumab) are recommended according to availability and patient factors; conventional immunosuppressants remain alternatives when biologics are inaccessible. Guidance is provided for pediatric patients and for pregnancy and breastfeeding, including planning after ≥12 months of disease stability and early postpartum treatment resumption. These MENACTRIMS guidelines aim to improve NMOSD outcomes across the region by promoting accurate diagnosis and timely, effective therapy.

Keywords: Diagnosis; Treatment; Neuromyelitis Optica Spectrum Disorder; Guidelines; MENACTRIMS.

1. Introduction

Neuromyelitis Optica Spectrum Disorder (NMOSD) is a severe, relapsing, inflammatory disorder of the central nervous system (CNS) that predominantly targets the optic nerves and spinal cord[1]. The clinical presentation can be diverse and the condition is often misdiagnosed as multiple sclerosis(MS)[2] or other neurological disorders[3]. The discovery in 2004 of a highly specific biomarker of the disease, the AQP4-IgG that binds to water channels at the astrocytic end-feet, redefined the disease and allowed for a more accurate diagnosis. Recently, four monoclonal antibodies have been evaluated in large randomized controlled trials, leading to their approval by regulatory agencies in the United States, Europe, and other countries for the treatment of NMOSD.

The Middle East and North Africa (MENA) region faces unique challenges in the diagnosis and management of NMOSD due to variations in healthcare infrastructure, availability of specialized care, and regional differences in disease presentation. The aim of this consensus is to provide comprehensive, region-specific guidelines for the diagnosis and management of NMOSD, focusing on AQP4-IgG positive and seronegative NMOSD and does not cover MOG-associated disease (MOGAD), with the goal of improving patient outcomes through early diagnosis, appropriate differential diagnosis, effective treatment strategies, and adherence to international standards adapted to the regional context.

2. Consensus Methodology

The Middle East and North Africa Committee for Treatment and Research in Multiple Sclerosis (MENACTRIMS) invited a group of neurologists from different countries in the MENA region with experience in managing NMOSD to a workshop in Dubai, UAE in June 2024. The panel consisted of academic, hospital-based and community general neurologists with expertise in NMOSD to ensure a wide diversity of opinions. Panelists were selected based on predefined criteria, including extensive clinical experience in NMOSD, management of a significant number of patients with the disease in their respective centers, recognized expertise within the MENA region, and academic contributions to the field (research publications, teaching, and guideline development). Additional considerations included geographic representation to ensure regional applicability of the recommendations. The guidelines were divided into six sections: diagnostic criteria and differential diagnosis; current therapies; relapse treatment; pregnancy and

breastfeeding; pediatric NMOSD; and treatment recommendations by serostatus. After a plenary discussion, each section was assigned to a panel member to review and prepare final recommendations based on the most recent scientific evidence. The panel reconvened in January 2025 in Dubai, UAE, discussed all recommendations and after extensive deliberation agreed on all points with minimal disagreement or concerns. The final recommendations were based on expert consensus and literature review. A recommendation was approved if at least 80% agreement was achieved by open voting. Recommendations not reaching this threshold were revised and re-voted until consensus was achieved.

3. Diagnosis

Accurate diagnosis is critical for proper treatment and improved patient outcomes. The International Panel for neuromyelitis optica (NMO) Diagnosis (IPND) published revised criteria in 2015 to enhance diagnostic accuracy by incorporating serological, magnetic resonance imaging (MRI) and clinical characteristics[4]. A revision of the current criteria is expected to be published by the end of 2025.

3.1 Diagnostic Criteria

The IPND 2015 criteria categorize NMOSD into AQP4-IgG positive and AQP4-IgG negative/unknown ***(Table 1)***. The presence of AQP4-IgG is central to the diagnosis in many patients, but the criteria also recognize the need to diagnose NMOSD in the absence of these antibodies based on clinical and radiological features.

For patients who test positive for AQP4-IgG antibodies, a diagnosis of NMOSD requires at least one core clinical characteristic and exclusion of alternative diagnoses.

In patients who are AQP4-IgG negative or whose antibody status is unknown, the diagnosis of NMOSD requires:

- At least two core clinical characteristics meeting all of the following criteria:
    - At least one core clinical characteristic must be optic neuritis, acute myelitis with longitudinally extensive transverse myelitis (LETM), or area postrema syndrome (APS).
    - Dissemination in space, which means two or more different core clinical characteristics.

- Fulfillment of additional MRI requirements as applicable.

- Exclusion of alternative diagnoses.

At the time of publication of the 2015 criteria, approximately 30% of NMOSD patients tested negative for AQP4-IgG[4]. Subsequently, a proportion (up to 40%) of AQP4-IgG negative NMOSD were found to be myelin oligodendrocyte glycoprotein IgG (MOG-IgG)[5] positive and can now be classified as MOGAD [6]. Specific criteria for the diagnosis of MOGAD are now available combining clinical features and serological testing[7]. Patients with neither antibody are called double-seronegative NMOSD (ds NMOSD). It is increasingly evident that ds NMOSD is a syndrome with heterogeneous etiologies and might include not only inflammatory but genetic, metabolic and other causes. Accordingly, careful diagnostic work-up is essential before confirming diagnosis[8].

Cell-based Assays (CBAs) are strongly recommended in the IPND 2015 diagnostic criteria for testing for AQP4-IgG[4]. CBAs offer higher sensitivity (76.7%), and specificity (up to 100% in some studies) compared to Enzyme-linked immunosorbent assays[9] (47% and 85%, respectively). Different CBAs provide different sensitivities with fixed CBAs showing slightly lower sensitivity compared to live CBAs[10]. CBAs are widely available in the MENA region. We recommend using either live or fixed CBAs, rather than ELISA, in testing for AQP4-IgG. AQP4-IgG should be ideally tested during a relapse before any immunotherapy, including corticosteroids, is initiated. CSF testing is not reliable[11].

3.2 Red Flags in Diagnosing NMOSD/ Differential Diagnosis

Accurate differential diagnosis is essential to distinguish NMOSD from other neurological disorders that have overlapping symptoms but require different treatment approaches. Key differential diagnoses include MS, MOGAD and acute disseminated encephalomyelitis (ADEM), although other entities should be considered such as vasculitis, CNS infections, and malignancies[11]. LETM, a core clinical presentation of NMOSD, can be seen with other disorders including autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy, neurosarcoidosis, Sjögren syndrome, systemic lupus erythematosus, Behçet disease, paraneoplastic myelitis, post-

infectious myelitis, acute spinal cord infarction and dural arteriovenous fistula[12]. It is of note that 14% of NMOSD patients presenting with myelitis exhibit a short segment lesion on MRI[13]. APS, another core clinical presentation of NMOSD is seen in 9-14% of patients, and presents with nausea, vomiting and hiccups. It is frequently misdiagnosed initially as a gastroenterological disorder[14]. The comparative clinical, imaging, and laboratory features of NMOSD, MS, MOGAD, and ADEM are summarized in ***Table 2***.

3.2.1 Multiple Sclerosis

MS is the most common differential diagnosis of NMOSD due to their overlapping clinical presentations, including optic neuritis and transverse myelitis. The newly published 2024 McDonald criteria will assist in distinguishing between the two diseases more effectively, particularly through the use of highly specific MRI biomarkers, including the central vein sign and paramagnetic rim lesions [15]. However, there are several distinguishing features:

- MRI characteristics: MS and NMOSD can be differentiated based on distinct MRI findings. MS typically presents with multifocal brain lesions, often located in periventricular, juxtacortical, and infratentorial regions[16]. Specific brain MRI characteristics that suggest MS include lesions in the inferior temporal lobe adjacent to the lateral ventricle, cortical/juxtacortical lesions, and Dawson's finger-type lesions[17]. Typical MRI findings in NMOSD include longitudinally extensive transverse myelitis, large confluent hemispheric lesions, lesions involving the dorsal medulla, long corticospinal tract lesions, thalamic and periependymal lesions, and optic nerve lesions extending over more than half the optic nerve or involving the optic chiasm[16].
- Cerebrospinal fluid (CSF) Findings: Oligoclonal bands are commonly found in the CSF of MS patients (90-95%) but are less frequently seen in NMOSD (20-30%)[18]. Additionally, unlike MS, CSF tests in NMOSD often reveal elevated pleocytosis, occurring in about 35% of cases, with a predominance of neutrophils or eosinophils. Another distinguishing feature is the increased CSF level of interleukin-6 (IL-6) found in NMOSD. Absence of CSF oligoclonal bands supports a diagnosis of NMOSD over MS[18].

- Clinical features: Relapse patterns differ significantly between MS and NMOSD. An analysis of 75 NMOSD cases and 101 age- and sex-matched MS controls from Australia and New Zealand revealed that while spinal cord and optic neuritis attacks were common in both conditions, optic neuritis and area postrema relapses were more frequent in NMOSD. NMOSD relapses were more severe as shown by higher level and longer duration of disability and higher frequency (time between relapses was 10.6 months in NMOSD compared with 18.0 months in MS), often requiring acute immunotherapies and showing less complete recovery. In addition, the course of NMOSD is mainly relapsing without evidence of progression, while MS is characterized by progressive disability at different stages of the disease[19].

3.2.2 Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease

MOGAD shares many clinical features with NMOSD, including optic neuritis and myelitis. However, there are many distinguishing features:

- MRI Characteristics: Both MOGAD and NMOSD show optic nerve lesions, but bilateral optic neuritis is more common in MOGAD (63 vs 25%) and perineural optic nerve enhancement is frequently seen. MOGAD often exhibits deep white matter lesions and leptomeningeal enhancement, which are less common in NMOSD[20]. NMOSD typically shows lesions in periependymal, periaqueductal, and hypothalamic areas while cortical subcortical and juxtacortical lesions are more frequent in MOGAD[20]. LETM is common in both MOGAD and NMOSD, but isolated conus medullaris lesions are more suggestive of MOGAD while cord atrophy is more pronounced in NMOSD. Resolution of spinal lesions is more common in MOGAD, whereas NMOSD lesions tend to persist.
- Serological testing: Serum AQP4-IgG are highly specific for NMOSD and high titers MOG-IgG (>1:100) are strongly suggestive of MOGAD. Low titers MOG-IgG (< 1:100) are non-specific and can be seen in other CNS demyelinating disorders. In MOG-IgG seronegative patients with clinical and MRI features suggestive of MOGAD, CSF testing for MOG-IgG can be used to support the diagnosis[7].
- Clinical features: NMOSD is much more common in women compared to MOGAD with a female to male ratio of 9:1 and 1:1, respectively. MOGAD patients generally

have better prognosis and a higher likelihood of recovery from relapses compared to NMOSD[21]. Nearly 50% of patients with MOGAD follow a monophasic course as opposed to a relapsing course with NMOSD.

3.2.3 Acute Disseminated Encephalomyelitis

ADEM is a CNS inflammatory demyelinating disease that usually presents as a monophasic illness with multifocal neurological symptoms following an infection or vaccination. Key differences with NMOSD include:

- Age of Onset: ADEM predominantly affects children, while NMOSD can occur at any age but is more common in adults[20].
- Course of Disease: ADEM is typically monophasic, whereas NMOSD is characterized by recurrent attacks[20, 22].
- MRI Findings: Patients with ADEM exhibit brain lesions that closely resemble the confluent white matter lesions seen in NMOSD[23]. However, thalamic and internal capsule involvement could differentiate pediatric-onset NMOSD from ADEM[24].

3.3 Recommendations

- The diagnosis of NMOSD should be made based on the IPND 2015 criteria.
- The differential diagnosis primarily includes MS, MOGAD and ADEM and requires a combination of clinical evaluation, antibody testing, and MRI characteristics to make a definite diagnosis.
- Cell-based assays, preferably live, are recommended in testing for AQP4-IgG and should be ideally obtained during a relapse before initiation of immunotherapy.

4. Treatment

4.1 Treatment of Relapses

Relapses in NMOSD are usually more severe than MS[22]. The outcome of untreated NMOSD relapses is poor, with only 21.6% of patients making full recovery and 6% displaying no improvement at all[25]. However, prompt initiation of therapy in acute attacks and early escalation significantly improves outcomes.

The standard of care for acute attacks in both AQP4-IgG positive and ds NMOSD includes high-dose corticosteroids and plasma exchange (PE)[26]. Intravenous methylprednisolone (IVMP) is usually administered at a dose of 1000 mg per day for 3-5 days, followed by an oral corticosteroids taper (starting with 1 mg/kg/day and then tapered to 10-15 mg/day within 2-3 weeks). Low-dose oral corticosteroids for up to 3-6 months are beneficial in preventing early subsequent attacks, although there is a lack of prospective studies to support this approach[27]. The duration of low-dose corticosteroid maintenance treatment depends on the AQP4-IgG serostatus, disease activity, mode of action and expected time to subsequent immunotherapy.

If patients do not respond adequately to methylprednisolone within the first few days, early rescue therapy with PE, should be administered[25, 28-30]. Most studies with PE have been conducted with an average of 5 cycles either daily or every other day, although up to 10 cycles have been used[25, 31]. Several retrospective studies have shown that early use of PE leads to better outcomes[25, 27, 28, 32, 33]: if initiated within 2 days of symptom onset, up to 40% of patients would make a full recovery as opposed to 3.7% if treatment is delayed for 7 or more days[25, 34, 35]. Accordingly, early PE, preferably within 2 days of onset, either alone or as adjunctive therapy (add-on to corticosteroids) should be considered in patients with disabling relapses[25]. In one study, patients with myelitis responded better to PE than IVMP as initial therapy[25]. A repeated treatment course with either high dose intravenous corticosteroids or PE improved outcomes and lowered the number of non-responders[25].

No randomized clinical trials (RCTs) have investigated the effectiveness of intravenous immunoglobulin (IVIG) for acute NMOSD relapses, but IVIG may be a suitable option when PE is unavailable or contraindicated. A study showed that the combination of IVIG and high-dose corticosteroids led to higher chance of clinical recovery, whereas IVIG alone was linked with worsened clinical outcomes[36]. A recent study showed that PE was more effective than IVIG in reducing antibody concentrations as an add-on therapy in AQP4-IgG positive NMOSD patients[37].

Other therapeutic strategies such as early use of anti-CD20 or anti-complement therapies have been reported in single case series to lead to favorable outcomes in acute attacks[38] [39-41]. Future therapies may also include antibodies against the neonatal Fc receptor, which are currently being studied in an open-label trial (NCT06497374).

4.2 Recommendations

- Treatment with high-dose corticosteroids and/or PE should be initiated as early as possible. Early treatment of relapses is essential for ensuring proper recovery.
- Patients with inadequate response to high-dose corticosteroids should be started on PE therapy early on.
- PE should be used as initial therapy, preferably within 2 days, in patients with:
    - Incomplete response to corticosteroids in previous relapses
    - Adequate response to PE during previous relapses
    - Disabling relapses
- Combined treatment with high-dose corticosteroids and PE may be used in disabling relapses.

4.3 Long-Term Immunotherapy

Conventional immunosuppressants such as azathioprine (AZA), mycophenolate (MMF), methotrexate (MTX), rituximab (RTX), mitoxantrone and cyclophosphamide have been successfully used to prevent NMO relapses. Recently, four monoclonal antibodies have been evaluated in large randomized controlled trials, leading to their approval by regulatory agencies in the United States, Europe, and other countries. These include complement inhibitors (eculizumab and ravulizumab), IL-6 inhibitors (satralizumab), and a novel anti-CD19 monoclonal antibody (inebilizumab).

4.3.1 Treatment of Anti-AQP4 Positive NMOSD

Patients with AQP4-IgG positive NMOSD are at increased risk of relapses[42, 43], and relapses are usually devastating with poor recovery[44] leading to increased mortality[45, 46]. Accordingly, relapse prevention is the cornerstone of management of AQP4-IgG positive NMOSD. The panel agreed that all patients with AQP4-IgG positive NMOSD should be treated with chronic immunosuppression to prevent relapses and preserve neurologic function. Various immunomodulators and immunosuppressants have been used, with variable efficacy and safety profiles. Traditional immunosuppressants, such as corticosteroids, azathioprine,

mycophenolate mofetil, cyclophosphamide, and mitoxantrone, have been used for the past two decades for the management of NMO, and therefore have a longer track record of safety. In the past two decades, there has been increasing use of rituximab (anti-CD20) and tocilizumab (IL-6 inhibitor) as off-label therapies, both of which showed a high degree of efficacy. More recently, the new approved monoclonal antibodies have started to gain popularity, unfortunately limited by their expensive pricing.

4.3.1.1 Corticosteroids

The long-term use of corticosteroids for relapse prevention in NMOSD should be discouraged due to the associated adverse events. Most experts recommend maintaining oral prednisone (1 mg/kg/day) until an immunotherapy is initiated and has reached its expected efficacy before a slow taper is initiated. Care has to be taken in prescribing high-dose corticosteroids in elderly patients or patients at risk of osteoporosis and other corticosteroids complications[47]. Adjunct low-dose prednisone can be used as an add-on in selected cases if relapses are not controlled with conventional immunosuppressants and higher efficacy treatments are not available[48].

4.3.1.2 Conventional Immunosuppressants

AZA, MMF, MTX, mitoxantrone and cyclophosphamide have been successfully used to prevent NMO relapses[49-53]. The evidence of efficacy comes mostly from uncontrolled case series or retrospective case-controlled studies.

AZA is a purine synthesis inhibitor that interferes with cell proliferation, especially lymphocytes[54]. It is one of the most commonly used medications to prevent NMO relapses. The optimum dosage of AZA in NMOSD is not well-studied, but most experts recommend 2-3 mg/kg/day[55, 56]. An increase in the red blood cell mean corpuscular volume (MCV) by 5 points above baseline has been associated with a lower risk of relapses[57]. The full biological effect of AZA is achieved around 4–6 months after treatment initiation. Accordingly, continued use of prednisone is recommended until AZA is fully effective [55]. A large-scale single-center study of patients with NMOSD (about 50% AQP4-IgG positive) showed that AZA reduced the risk of expanded disability status scale (EDSS) progression by 80% over a five year period [58]. One of the largest experiences with AZA in NMOSD to date was reported by Costanzi et al., who retrospectively reviewed 99 NMO/NMOSD cases treated with AZA

over a fifteen-year period[57]. AZA, with or without corticosteroids, decreased annualized relapse rate from 2.20 to 0.52 over a median treatment duration of 22 months[57].

AZA has been shown in multiple studies to be inferior to rituximab and tocilizumab in preventing relapses and reducing disability[59-61]. In a randomized clinical trial, 54.3% of patients on AZA and 78.8% on rituximab were relapse-free[51]. In an open-label, multicenter, randomized Phase 2 study (TANGO study) comparing the efficacy of tocilizumab and AZA in severe NMOSD, only 14% of patients in the tocilizumab group experienced a first relapse, compared to 47% in the AZA group (hazard ratio [HR] 0.236 [95% CI 0.107– 0.518]; p<0-0001)[62].

The incidence of adverse events on AZA ranges from 6.5 to 43.8%[51, 57, 60, 63] including nausea, abnormal liver function tests, leukopenia, fatigue, hair loss and diarrhea. Serious adverse events include hepatotoxicity, bone marrow suppression and malignancies (lymphoma reported in 3% of patients)[57]. Cumulative doses of 600 g should not be exceeded due to possible increased risk of malignancy[64]. Thiopurine S-methyltransferase polymorphisms appear to modify the risk of side effects[65]. The risk of treatment failure on AZA is higher in patients with history of severe relapses or high annualized relapse rate (ARR)[66]. Compared to other steroid-sparing agents, azathioprine has the advantage of lower cost and good safety profile during pregnancy.

MMF is another commonly used immunosuppressant in the management of NMOSD. It is an inhibitor of inosine-5′ —monophosphate dehydrogenase which interferes with proliferation of B and T lymphocytes. The efficacy of MMF has been established in multiple observational studies in both AQP4-IgG positive and negative NMOSD. A meta-analysis involving 930 patients reported an average reduction in ARR of -1.17[52]. Another study involving 200 patients found a mean decrease in ARR by 1.13 with a mean EDSS reduction of 0.85 points (95% CI 0.36–1.34)[67]. A study comparing low-dose RTX and MMF in Chinese patients with NMOSD found that both treatments were effective and tolerable, although rituximab showed a better reduction in ARR[68]. MMF is commonly prescribed at a dose of 1500 – 3000 mg per day, targeting an absolute lymphocyte count of 1000 – 1500 to cells/μL for maximal efficacy and minimal adverse events. MMF was associated with an increased risk of lymphoma in transplant patients and non-melanoma skin carcinoma[69].

MTX, an inhibitor of dihydrofolate reductase, is considered a safe alternative to AZA and MMF, although it is less commonly used in NMOSD due to the limited number of observational studies[70, 71]. A study, involving 14 patients with NMOSD treated with MTX demonstrated a 64% reduction in ARR and a relapse freedom rate of 75%[50]. Potential side effects of MTX include bone marrow suppression and elevated liver function tests.

For severe and disabling relapses, pulse cyclophosphamide or mitoxantrone have been used with reported efficacy, mostly in small reports[49, 53]. Given the high toxicity of both agents, their use became limited to scenarios where other alternatives are unavailable.

4.3.1.3 Rituximab

RTX is a chimeric monoclonal IgG antibody targeting the CD20 surface antigen on B lymphocytes. RTX has been one of the most effective therapies in NMOSD for the last two decades. It is approved in Japan for the prevention of relapses in patients with NMOSD but is still used off-label in other parts of the world based on experts' opinion and consensus guidelines[34, 54]. In a prospective open-label study of 30 patients treated with RTX, relapse rate was reduced by 88%, and 70% of patients became relapse-free over 24 months[72]. Disability either improved or stabilized in 97% of patients and AQP4-IgG declined significantly. A retrospective review of 100 patients with relapsing NMOSD treated with RTX for at least 6 months and a follow-up period of more than 5 years, ARR was reduced by 96% and disability improved or stabilized in 96% of patients[73].

An open label randomized clinical trial conducted in Iran included 86 NMOSD patients (33 AQP4-IgG positive), randomized to receive either AZA or RTX[51]. The mean ARR in the AZA group decreased from 1 (0.38) to 0.51 (0.55) ($p<0.001$) and from 1.30 (0.68) to 0.21 (0.42) in the RTX group ($p<0.001$). Nineteen patients (54.3%) on AZA and 26 (78.8%) on RTX were relapse free ($p= 0.033$). The authors concluded that RTX was significantly more effective than AZA[51].

A multicenter, randomized, double-blind, placebo-controlled trial was conducted in AQP4-IgG positive NMOSD patients in Japan (RIN-1 study)[74]: 38 participants were randomly allocated to either rituximab (n=19) or placebo (n=19). Seven relapses occurred in the placebo

group, and none in the rituximab group (p=0·0058). This study, however, was limited by its small sample size and inclusion of participants with mild disease activity. A recent systematic review and meta-analysis of RTX in NMOSD included 29 studies and 732 patients[75]. It showed that RTX reduced both EDSS and ARR by an average of 0.57 (95%CI, -0.69 to -0.44) and 1.57 (95%CI, -1.78 to -1.35) respectively. Side effects of RTX include infusion reactions, infections (including progressive multifocal leukoencephalopathy with an estimated risk of 1:20,000), myelosuppression, hepatitis B and tuberculosis reactivation[76]. Hypogammaglobulinemia remains a concern, especially with long-term use[77]. A retrospective study of 169 NMOSD patients treated with RTX found that serum IgG levels declined significantly after two years, dropping by 2-8% annually for eight years before plateauing at ten years[78]. The proportion of patients with low IgG (<6 g/L) increased from 1.2% after one year to 41% after 14 years.

The dosing of RTX in NMOSD has been variable across centers varying from 500 to 2000 mg administered every 6-12 months. A study comparing 2000 and 1000 mg every six months in 161 patients with NMOSD or MS found that the rate of B-cell repopulation was similar between the two groups and concluded that 1000 mg every 6 months was sufficient[79].

A retrospective analysis showed that extended interval dosing of RTX guided by B-cell repopulation (>1%) had a similar effect on relapse rate compared to standard every 6 months dosing in patients with AQP4-IgG positive NMOSD[80]. It is of note that in this study each RTX cycle consisted of 2000 mg. An observational study involving 37 patients, 73% of whom were AQP4-IgG positive, found that the ARR after RTX treatment was significantly low (0.136). The RTX dosing regimen consisted of an initial 1000 mg dose followed by maintenance doses of 500 mg every six months or upon B-cell repopulation[81]. Another retrospective analysis of 136 NMOSD patients treated with RTX in China showed that an ultralow-dose regimen (100-300 mg based on B-cell repopulation was not inferior in relapse prevention to a low-dose regimen (500 mg every six months)[82]. Another large prospective study examined the efficacy of low-dose RTX administered at a dose of 100 mg once weekly for three weeks as induction therapy, followed by maintenance of 100 mg once every six months according to the percentages of circulating B-cell subsets and patient's preference[83]. There was a significant reduction in ARR, with a 67.6% relapse-free rate. Rather than dosing

by the total CD19-positive B-cells, Bruschi et al. suggested that dosing based on CD27-positive memory B-cells has resulted in fewer infusions while maintaining efficacy[84].

4.3.1.4 Inebilizumab

Inebilizumab was approved as monotherapy in adults with AQP4-IgG positive NMOSD. It is a humanized monoclonal antibody that depletes B lymphocytes by binding to the CD19 molecule leading to broader depletion of B-cell lineage including plasma blasts, potentially offering a higher efficacy than anti-CD20 agents[85]. It also offers an advantage over RTX in patients with FCGR3A polymorphism, who are relatively resistant to RTX. The recommended initial dosing consists of two 300 mg intravenous infusions administered two weeks apart followed by a single dose of 300 mg, every six months[34, 86, 87]. In a phase II/III placebo-controlled study (N-Momentum), 12% of patients on inebilizumab sustained a relapse compared to 39% receiving placebo (HR= 0.272; 95% CI= 0.150–0.496; $p<0.0001$). These results were particularly significant in the anti-AQP4 positive group (11% versus 42%; HR=0.227; 95% CI= 0.121–0.423; $p<0.0001$)[88]. Mean EDSS scores improved with longer-term treatment. In 13 patients with prior use of rituximab, the ARR on inebilizumab was similar to that of participants without prior rituximab use (0.08 vs 0.10)[89].Treatment efficacy in the AQP4-IgG group could not be determined due to the small sample size[88, 90]. Serious adverse events occurred in 5% of patients receiving inebilizumab and 9% of patients on placebo, with two deaths in the open-label period, one in each arm. Inebilizumab may have a potential advantage over RTX due to its different biological targets. Among the seventeen participants in the trial who were initially treated with RTX, 13 were randomly assigned to the inebilizumab treatment group. ARR was reduced from 0.78 to 0.08 upon switching to inebilizumab. Treatment efficacy was comparable for patients with and without prior RTX use. The long-term efficacy and safety of inebilizumab was investigated in 75 AQP4-IgG positive NMOSD patients receiving treatment for more than four years (mean treatment duration of 4.6 years), as an open-label extension of the N-Momentum trial[91]. Sixty five patients were initially assigned to the inebilizumab group and 10 to the placebo group. A total of 83% were relapse free with stable levels of disability throughout the study extension. Inebilizumab was well-tolerated with only 2.7% of patients experiencing serious and treatment-related side

effects. No deaths or progressive multifocal leukoencephalopathy (PML) cases were reported during the extension period.

Before starting RTX or inebilizumab, it is essential to exclude any active infection and screen for latent infections including hepatitis B and C and tuberculosis. Ensure that vaccinations are up to date, particularly live vaccines. Any live vaccines should be administered four weeks before therapy as they are contraindicated during treatment[92].

4.3.1.5 Eculizumab and Ravulizumab

Eculizumab was the first U.S. Food and Drug Administration [92] approved therapy for adults with AQP4-IgG positive NMOSD [92] and is currently available in many countries in the MENA region. It is a monoclonal antibody specifically targeting complement protein C5, blocking its cleavage into C5a and preventing the formation of the membrane attack complex[93]. The clinical efficacy of eculizumab was established in the PREVENT trial, a randomized, double-blind placebo-controlled trial, including 143 AQP4-IgG positive NMOSD patients[2]. Patients on eculizumab showed a 94.2% reduction in relapse rate compared to placebo over 4 years although MRI was not used to adjudicate events (NCT01892345).There were no cases of meningococcal infection during the trial. The recommended dosing of eculizumab is 900 mg intravenous weekly for 4 weeks followed by 1200 mg IV biweekly[94]. Following the approval of eculizumab, both FDA and European Medicines Agency [25] approved ravulizumab, a humanized, long-lasting complement inhibiting monoclonal antibody, for the treatment of adults with AQP4-IgG positive NMOSD. Ravulizumab is currently available in many countries in the MENA region. Ravulizumab was bioengineered by substituting four amino acids in the eculizumab heavy chain frame which extended its half-life, allowing its administration every eight weeks[95]. A phase 3, open-label clinical trial (CHAMPION-NMOSD) compared 58 patients with AQP4-IgG positive NMOSD to the 47 patients in the placebo arm of the PREVENT trial[96]. None of the patients in the treatment arm had a relapse after a minimum of 50 weeks (compared to 20 in 47 PREVENT placebo patients during the same period of time). MRI was required to adjudicate events in this study. A network meta-analysis on the trials data of eculizumab, inebilizumab and satralizumab, suggested that complement inhibition with eculizumab may be more effective in preventing NMOSD attacks than treatment with inebilizumab or satralizumab[97]. The safety profile was

acceptable with two patients developing a meningococcal infection. The recommended dosing of ravulizumab is weight-based and is administered intravenously every 8 weeks[95].

Both eculizumab and ravulizumab have a rapid onset of action and induce continuous near-complete inhibition of C5 activity after the first infusion[98].

As with all complement-inhibiting therapies, patients should be vaccinated against *N. meningitidis* at least 2 weeks prior to the first infusion. Alternatively, if therapy needs to be started urgently, patients must receive antibiotic prophylaxis until at least 2 weeks after completed vaccination[99].In patients receiving long-term eculizumab therapy, meningococcal vaccination should follow current recommendations, including booster doses of the MenACWY vaccine every 5 years for the duration of treatment[100]. Vaccination and/or antibiotic prophylaxis reduces but does not eliminate the risk of invasive meningococcal infection; therefore, careful clinical vigilance and patient education regarding early symptoms of meningococcal disease are required.

4.3.1.6 Satralizumab and Tocilizumab

Interleukin 6 (IL-6) is known to be elevated in NMOSD. It plays a vital role in the survival of plasma blasts, increases their secretion of AQP4-IgG[101] and contributes to dysfunction of the blood-brain barrier allowing for increased leukocyte transmigration[102]. A phase 2 open-label randomized trial (TANGO) conducted in China compared IV tocilizumab (8 mg/kg every four weeks), an anti-IL-6R monoclonal antibody, and AZA in patients with NMOSD. More than 85% of the patients were AQP4-IgG positive. Tocilizumab significantly prolonged the time to relapse (median of 78.9 weeks vs 56.7 weeks in AZA) and reduced the relapse rate to 14% compared to 47% with AZA[62]. A subcutaneous formulation of tocilizumab appears to be effective, based on findings from a small retrospective series involving seven patients with AQP4-IgG positive NMOSD[103]. It is of note that the use of tocilizumab for NMOSD is considered off-label in most countries.

Satralizumab is a humanized anti-IL-6 receptor monoclonal antibody approved for the treatment of AQP4-IgG positive NMOSD in adults and children aged ≥ 12 years[104]. The recommended dose is 120 mg by subcutaneous injection at weeks 0, 2, and 4, and then every 4 weeks thereafter[104].

The SAkuraSky was a phase 3, randomized, double-blind, placebo-controlled clinical trial which included patients aged between 12 and 74 years and who had either AQP4-IgG positive or negative NMOSD[105]. Satralizumab was added to baseline immunosuppressive treatments, which included AZA, MMF, and oral corticosteroids, while the use of anti-CD20 agents was not authorized before study enrollment. The study met its primary endpoint with a lower proportion of patients experiencing a first relapse compared to placebo (HR= 0.38; 95% CI= 0.16 to 0.88; p= 0.02)[105]. The SAkuraStar was a phase 3, international, randomized, double-blind, placebo-controlled study of satralizumab as monotherapy for the treatment of patients, aged between 18 and 74 years, who had either AQP4-IgG positive or AQP4-IgG negative NMOSD[106]. Satralizumab was associated with a significant reduction in relapse rate compared to placebo (HR=0.45, 95% Cl= 0.23–0.89; p=0.018). Similar results were obtained in a Japanese real-world cohort (n=131) in which 95.4% of patients on satralizumab were relapse-free over a median duration of 197 days[107]. Satralizumab had a favorable safety profile as the incidence of serious adverse events and adverse events leading to withdrawal was similar between the two arms in both trials[105, 106]. The safety profile of satralizumab, whether as monotherapy or in combination with immunosuppressive treatments, was unchanged during the open-label extension with most adverse events being mild to moderate[108, 109]. The most common adverse events were nasopharyngitis, upper respiratory and urinary tract infection. Injection-related reactions were mild and did not lead to treatment discontinuation. Drop in neutrophil and platelet counts, and elevation in liver enzymes, were transient[108]. It is recommended that patients receive all appropriate vaccinations before starting satralizumab. Screening for tuberculosis is also advised prior to initiation.

4.3.1.7 Autologous hematopoietic stem cell transplantation

Autologous hematopoietic stem cell transplantation (AHSCT) is an emerging therapeutic approach for NMOSD. The process involves harvesting hematopoietic stem cells from the patient's bone marrow or peripheral blood followed by high-dose chemotherapy to ablate the existing immune system. The collected stem cells are reintroduced into the patient's body to regenerate a new less autoreactive immune system. AHSCT is typically reserved for patients with severe, refractory NMOSD who have not responded adequately to standard treatments[5].

In a retrospective multicenter study, the European Society for Blood and Marrow Transplantation (EBMT) assessed the efficacy and safety of AHSCT in 16 patients with NMOSD refractory to treatment[110]. After a median follow-up of around 4 years, 3 patients were disease-free while 13 required further treatments due to relapses or disability progression. Burt et al. enrolled 12 patients with NMOSD without other associated autoimmune disorders (11 were AQP4-IgG positive) in a prospective open-label trial of AHSCT. Out of 11 patients with more than 5 years follow-up, 80% were free of relapses and off treatment. Interestingly, 9/11 AQP4-IgG positive patients became seronegative[111].

AHSCT represents a promising option for patients with refractory NMOSD, offering potential long-term remission and improved quality of life. However, due to the risks involved, it is crucial to carefully select appropriate candidates and provide thorough pre- and post-transplant care. In case of breakthrough disease on at least two monoclonal antibodies including a complement inhibitor, patients should be referred to a specialized center for the possibility of AHSCT. Anti-BCMA CAR-T cell therapy represents a promising emerging option for refractory cases in the future[112].

4.3.1.8 Switching Therapies

Studies on switching between immunotherapies in NMOSD are limited. Switching treatment is usually due to breakthrough disease or side effects. In case of breakthrough disease, the most common switch is from RTX, which is widely used in the MENA region, to one of the newly approved monoclonal antibodies. In the PREVENT and CHAMPION-NMOSD trials a minimal washout period of 3 months was required before shifting from RTX to eculizumab or ravulizumab, respectively[2, 96]. Safety analysis did not show any increase in risk of infection. The MOMENTUM, TANGO and SAkura trials required a minimal washout period of 6 months before shifting from RTX to inebilizumab, tocilizumab and satralizumab, respectively and did not show any major safety concerns[62, 88, 105]. However, when switching therapies due to breakthrough disease, it is probably unsafe to go for 3-6 months washout periods. Earlier switching taking into consideration the patient's age, relapse severity, previous drug half-life and time to onset of action of the new treatment would be more appropriate. In case of breakthrough disease on conventional immunosuppressants, a direct switch to monoclonal

antibody therapy without prolonged washout is generally recommended, as a long treatment gap carries high relapse risk. When switching from conventional immunosuppressants because of infection, intolerance, bone marrow suppression, or hepatotoxicity, conventional agents should be discontinued immediately and another therapy initiated once infection or toxicity is controlled. Overlap with low-dose prednisone during the transition period may be used until the biologic reaches therapeutic.

4.3.1.9 Recommendations

- The monoclonal antibodies rituximab, eculizumab, ravulizumab, inebilizumab, tocilizumab or satralizumab should be offered as first line therapy in patients with AQP4-IgG positive NMOSD based on availability and affordability.
- Rituximab is off-label in most countries but widely used due to cost considerations
- Rituximab redosing based on B-cell repopulation is acceptable but should be carried out in specialized centers with expertise in managing NMOSD.
- In patients with disabling relapses or poor recovery, complement inhibitors can be offered as first line therapy as they have shown probably the highest efficacy in the initial trials, although comparing different trials with different study populations, inclusion criteria and relapse definitions is not ideal.
- The use of conventional immunosuppressants as monotherapy should be limited to patients who are stable on them or unable to receive monoclonal antibody therapies.
- Breakthrough disease was defined as a relapse during therapy despite sufficient time to expect full action,
- In case of disease breakthrough on conventional immunosuppressants, escalation to one of the monoclonal antibodies is recommended.
- In case of disease breakthrough on a monoclonal antibody, switching to another monoclonal antibody with a different mechanism of action is recommended. Conventional immunosuppressants can also be used as an add-on if other monoclonal antibodies are inaccessible or unaffordable.

- Maintenance with oral prednisone (1mg/kg/day) is recommended following the first relapse or upon switching therapies until a long-term treatment is initiated and has reached its expected efficacy before a slow taper is initiated.

4.3.2 Discontinuation of Immunotherapy

NMOSD often requires long-term immunosuppressant therapy to prevent relapses. However, there is no consensus about treatment duration. The main concern in discontinuing therapy is the risk of relapse, as a single relapse can result in significant disability. A recent French study showed that RTX de-escalation (including increased infusion intervals or switching to oral therapies) or discontinuation in AQP4-IgG positive and ds NMOSD patients is associated with increased risk of relapses in the following 12 months[113]. A study involving 17 patients with AQP4-IgG positive NMOSD who discontinued immunosuppressive therapies after being relapse-free for at least three years found that approximately 82% experienced a relapse. Notably, relapses occurred even in patients who had remained relapse-free for five years before stopping treatment[114]. However, few other studies reported prolonged disease-free periods off treatment[115]. Pandit et al. reported remissions for up to 20 years in AQP4-IgG positive patients off treatment[116]. Prolonged remissions were also reported in few cases following discontinuation of rituximab[117] .However, such cases are rare, and the long-term risks of immunotherapy are small compared to the risk of a new disabling relapse in AQP4-IgG positive disease.

4.3.3 Recommendations

- In patients with AQP4-IgG positive NMOSD, treatment should be maintained for as long as possible.
- Patients not receiving treatment should be closely monitored for any evidence of disease reactivation.

4.3.4 Treatment of ds NMOSD

Patients with ds NMOSD and inflammatory features (acute onset, typical imaging, CSF oligoclonal bands (OCB), coexisting autoimmunity, steroid and PE response... etc.) as opposed to genetic, metabolic or other causes, can be divided into monophasic (around 10%) and relapsing groups.

4.3.5 Choice of Disease-Modifying Therapy (DMT) in Relapsing ds NMOSD

No treatment is currently approved for ds NMOSD. The pivotal trials of satralizumab and inebilizumab included ds NMOSD cases but the numbers were too small to draw any conclusions. Since the underlying mechanisms of inflammation can be heterogeneous, it is logical to use broad conventional immunosuppressants with effect on both T and B-cell pathways. Typically, these include corticosteroids, MMF, AZA and MTX[34, 118]. Alternatively, a B-cell depleting therapy such as RTX is reasonable. In a multicenter retrospective study of ds NMOSD patients treated with RTX or MMF, ARR declined from 1.93 to 0.12 and from 1.45 to 0.30, respectively[119]. In another retrospective review of 74 patients with ds NMOSD, ARR decreased from 0.3 to 0.2 on RTX, from 0.9 to 0.5 on AZA, and from 0.9 to 0.4 on MMF[120]. In patients with breakthrough disease on first line therapies, tocilizumab has been shown to be effective[121]. If relapses occur on these therapies, tocilizumab, a combination of rituximab and oral immunosuppressants, cyclophosphamide, mitoxantrone or AHSCT can be tried.

4.3.6 Should DMT Be Initiated after the First Attack in ds NMOSD?

Initiating long-term DMT after the very first relapse in ds NMOSD is controversial as some patients may have only a one-off event e.g., a post infectious or post vaccination demyelinating episode[34, 122]. Some cases may not even be inflammatory. There are currently no reliable predictors of future relapses in ds NMOSD. However, the panel felt that in view of the disabling nature of NMOSD relapses, treatment should be offered early on irrespective of serostatus. Careful clinical and MRI follow up is required in patients on no treatment. An arbitrary clinical and radiologic follow up of 5 years is considered reasonable before labelling ds NMOSD as monophasic and discontinuing follow up[4].

4.3.7 Recommemdations

- Initiate treatment in patients with ds NMOSD following the first attack.
- Recommend periodic reevaluation in persistently ds NMOSD with monophasic course for need of treatment continuation.
- Initiate treatment with rituximab, mycophenolate, azathioprine or methotrexate

- In case of breakthrough disease, tocilizumab, a combination of rituximab and oral immunosuppressants, cyclophosphamide or AHSCT can be tried. Eculizumab, ravulizumab, or satralizumab can also be used.

5. Special Populations

5.1 Pediatric NMOSD

NMOSD is rare in the pediatric group accounting for around 3-5% of cases[123]. Pediatric patients have been poorly represented in the pivotal trials of new monoclonal antibodies. In the absence of class I evidence, treatment of children with NMOSD relies on data from observational retrospective studies. In a retrospective review of 91 children with NMOSD (AQP4-IgG positive or ds NMOSD), the most commonly used treatments were RTX (n = 38), MMF (n = 16), AZA (n = 15), and IVIg (n = 9)[124]. Patients on RTX and MMF had the lowest ARR, followed by azathioprine and IVIG: 0.25, 0.33, 0.40 and 0.54 respectively.

In a multicenter retrospective study of 16 children with NMOSD, RTX led to significant reduction in ARR (p=0.003)[125]. Six patients were relapse-free during a mean follow-up of 6.1 years (range 1.6–13.6). Most relapses were associated with B-cell repopulation or depletion failure. In another observational study, five children with NMOSD had significant reduction in relapse rate on RTX. The attacks were also related to B-cell repopulation[125]. B-cell repopulation is highly variable in pediatric patients and is dose dependent. Monitoring of B-cell levels and individualized redosing has been suggested[126]. RTX has been used in pediatric patients for other indications and has overall a good safety profile in this age group. In a study following 144 children with various autoimmune and inflammatory disorders receiving RTX, adverse events occurred in 7.6% of patients including 2 deaths[127]. None had PML.

Satralizumab is a humanized anti-IL-6 receptor monoclonal antibody approved for the treatment of AQP4-IgG positive NMOSD in adults and children aged ≥ 12 years[104]. However, there is limited experience in using satralizumab as a first-line therapy for adolescents with NMOSD (4 adolescents in SAkuraStar and none in SAkuraSky trials).

Tocilizumab is approved for pediatric use for treatment of systemic juvenile arthritis and polyarticular juvenile idiopathic arthritis. Breu et al. reported on two female adolescents with AQP4-IgG positive NMOSD who relapsed under RTX therapy and clinically stabilized after

switching to tocilizumab at a dose of 8mg/Kg [128].The recommended pediatrics dose of tocilizumab in juvenile rheumatoid arthritis and other autoimmune disorders is 8-12mg/Kg[129].
A single case report of a 12 year old child with severe AQP4-IgG positive NMOSD and initial worsening on high dose IV methylprednisolone and plasma-exchange, reported significant improvement of symptoms with gradual recovery over 10 weeks following treatment with eculizumab with two weekly doses of 600 mg followed by maintenance dosage of 900 mg at week 3 and every 2 weeks thereafter [130]. Serum AQP4-IgG titer dropped from >1:100000 to 1:100. Eculizumab has also been used in pediatric patients with atypical hemolytic uremic syndrome and showed a good safety profile[131]. As in adults, treatment should be preceded by meningococcal vaccine and/or antibiotic prophylaxis.
Ravulizumab has also been used in pediatric patients with atypical hemolytic uremic syndrome and has shown a good safety profile with the most common side effects being upper respiratory tract infection (40%) and oropharyngeal pain (30%) but no cases of meningococcal infections or deaths. Dosage and dosing interval used were based on patient's weight. [132]. No efficacy can be reported in NMOSD pediatric group due to lack of trials or even case reports.
Another single case report of a 14 year old boy with NMOSD and no improvement on IV methylprednisolone and IVIG, reported complete recovery on plasma-exchange followed by maintenance on prednisolone and satralizumab (120 mg/dose for 4 weeks). The child was relapse-free for 24 months[133].
There are currently no reports on the use of inebilizumab in pediatric patients with NMOSD or other autoimmune diseases. I-CAN is an ongoing phase II trial evaluating the safety of inebilizumab in patients between the age of 2 and 18 years (NCT05549258).
Due to the rarity of NMOSD in children, no clear guidelines regarding treatment discontinuation are available in the literature. However, in the large pediatric NMOSD cohorts reported, treatment was generally maintained[126, 134].
Acute relapses in children are usually managed like adults with IVMP and PE. The latter has also been shown to be effective and safe in pediatric NMOSD[135].

5.2 Recommendations

- Pediatric patients with NMOSD can be treated initially with rituximab, mycophenolate, azathioprine or methotrexate.

- In case of breakthrough disease on oral immunosuppressants, escalation to rituximab is recommended.
- Children above 12 years of age can be initiated on or escalated to satralizumab.
- In selected cases, especially in the case of breakthrough disease on initial therapies, ravulizumab, eculizumab, tocilizumab or satralizumab can be used.

5.3 Pregnancy and Breastfeeding

AQP4-IgG NMOSD has a strong female predominance (9:1 ratio), with a mean age at onset of 30– 40 years i.e.., during active childbearing years[136].

5.3.1 Impact of NMOSD on Pregnancy

NMOSD pregnancies are considered high risk with studies reporting increased rates of miscarriage, intra-uterine growth retardation, pre-eclampsia and eclampsia[137-142]. AQP4-IgG is expressed in the placenta and its binding by antibodies could lead to local inflammation and placental dysfunction[143]. AQP4-IgG can passively cross the placenta in the 2nd and 3rd trimesters and is detected in the newborn serum up to 3 months of age without clinical evidence of disease[143-145].

5.3.2 Impact of Pregnancy on NMOSD

Most reports point to increased risk of relapses during the pregnancy, especially in the last trimester with a marked increase in the postpartum period[138, 142, 146-149]. A higher risk of relapses during pregnancy and postpartum is associated with higher disease activity in the pre-pregnancy year, reduction or discontinuation of treatment, younger age at disease onset and higher titers of AQP4-IgG[148]. According to a recently published French consensus recommendations for pregnancy management in NMOSD, conception is advised after at least 12 months of disease stability[150]. Based on the aforementioned, high relapse rate and discontinuation of treatment before attempting conception carry a significant risk of relapses and disability[151] during pregnancy and the postpartum period. APS can be confused with hyperemesis gravidarum in early pregnancy since both cause severe nausea and vomiting. The area postrema is also implicated in the pathophysiology of hyperemesis gravidarum, particularly through the hormone GDF-15, which is produced by the placenta and binds to receptors in the area postrema.

5.3.3 Treatment of NMOSD During Pregnancy

AZA can be safely used during pregnancy[152, 153]. MMF and methotrexate are teratogenic[154-157] and should be discontinued before attempting conception. Non-fluorinated corticosteroids can be used alone or as add-on with other therapies such as AZA after careful benefit/risk ratio assessment. Corticosteroids may cause cleft palate if used during the first trimester and have been associated with intrauterine growth retardation and prematurity, and should be administered at the lowest effective dose[143].

Monoclonal antibody therapies provide a reasonable option for use during pregnancy planning [158]. IgG monoclonal antibodies do not cross the placenta during the first trimester, with active transfer beginning slowly at week 16[159]. Due to its long-lasting biological effect, pregnancy may be attempted 1 month after RTX infusion with minimal potential of fetal exposure, while offering immunomodulatory benefit for several additional months[160]. In a systematic review of 121 pregnancies in which RTX was used few weeks prior to or during pregnancy; 88 resulted in live births, 12 in spontaneous abortions, and 3 were preterm. B-cell counts were low in 39% of newborns but normalized within 6 months[161]. A German cohort of pregnant women exposed to anti-CD20 agents during pregnancy reported an increase in preterm births[162]. Another study of 153 pregnancies with maternal exposure to RTX, reported 90 live births, 22 preterm infants and one neonatal death. Eleven neonates had hematologic abnormalities, four had infections and another two had congenital anomalies[163]. In infants of mothers treated with anti-CD20 therapies, live vaccines (but not non-live vaccines) should only be administered after repletion of B-cells[58].

Satralizumab and inebilizumab product label advise against use during pregnancy[164]. Data on pregnancy outcomes with satralizumab and inebilizumab are very limited. However, inebilizumab like RTX, has the advantage of a prolonged biological activity and might be discontinued one month prior to conception.

A period of 3 months is usually required between the last infusion of tocilizumab and attempting conception[150]. However, tocilizumab has been used during pregnancy in women with rheumatoid arthritis without increased risk of congenital malformations, although the risk of spontaneous abortion and preterm birth was slightly elevated[165].

In a retrospective review of 75 pregnant women with atypical hemolytic uremic syndrome, treatment with eculizumab was safe[166]. In another study of 24 pregnant women with paroxysmal nocturnal hematuria treated with eculizumab, 85% had live births without evidence of congenital anomalies. Eculizumab half-life is ~12 days and can be given during pregnancy after a strict benefit/risk assessment [142]. Ravulizumab has a similar molecular structure to eculizumab and can probably be continued during pregnancy if benefits outweigh risk[34].

5.3.4 Treatment of NMOSD Relapses During Pregnancy

IVMP in short courses is considered safe during pregnancy. There might be an increased risk of cleft lip and palate with the use of corticosteroids during the first trimester[167-171]. PE can also be used safely during pregnancy. Risks and adverse events associated with PE appear to be similar with or without pregnancy[160, 172, 173].

5.3.5 Postpartum Management and Breastfeeding

Because of the high postpartum relapse rate, early resumption of immunotherapy after delivery is recommended[150]. The use of rituximab within 2 weeks of delivery reduced the risk of relapse to as low as 8.3%[34]. Monoclonal antibodies are large molecules and therefore their transfer to breast milk is minimal. Moreover, whatever is transferred to the infant will likely be destroyed in the gastrointestinal tract. The colostrum however, secreted during the first 7-10 days postpartum, is rich in antibodies, mostly IgA. Accordingly, monoclonal antibodies can be safely resumed in breastfeeding women with NMOSD 10-14 days post-delivery.

Very low or undetectable concentrations of AZA have been found in breastfed children of mothers taking AZA, with reassuring post-marketing safety data[174]. MMF and MTX are low molecular weight molecules and are easily transferable to breast milk. It is not recommended to use either one during breastfeeding.

5.3.6 Recommendations

- Pregnancy may be attempted after at least 12 months of disease stability.
- Conception can be attempted 1 month after the administration of rituximab or inebilizumab. Their long biological effect might control disease reactivation during pregnancy.

- Immunotherapy should not be discontinued or delayed to attempt conception.
- Rituximab, eculizumab, ravulizumab and tocilizumab can be continued during pregnancy if benefits outweigh risks after a thorough discussion with the patient.
- Azathioprine can be continued during pregnancy.
- Mycophenolate mofetil and methotrexate are teratogenic and should be discontinued prior to conception.
- There are no special recommendations regarding anesthesia type during delivery including epidural and spinal anesthesia.
- In case of fetal exposure to B-cell depleting therapies during pregnancy, we recommend testing for lymphocyte and B-cell counts in the newborn.
- If anti-CD20 therapies are continued during pregnancy, live attenuated vaccines should not be administered to infants before B-cell repletion.
- In case of treatment interruption during pregnancy, immunotherapy should be resumed shortly after delivery.
- Monoclonal antibodies can be administered safely to breastfeeding mothers 7-10 days after delivery.

6. Conclusion

With the emergence of MOGAD as a distinct entity and the approval of new therapies for NMOSD, diagnostic and treatment algorithms continue to evolve. Our current consensus guidelines synthesize current evidence and expert opinion to support accurate diagnosis and timely, effective treatment in the MENA region. Updated international diagnostic criteria incorporating recent advances and MOGAD, are forthcoming.

Statements and Declarations

Declaration of Competing Interest

The manuscript represents the views and opinions of the members involved in the development of the guidelines. All authors declare that they have no conflicts of interest related to the content of this manuscript.

Funding

This consensus workshop and manuscript development were fully funded by MENACTRIMS. No pharmaceutical company or external sponsor was involved in the organization, funding, or development of the manuscript.

Authors' Contributions

All authors participated as members of the panel of experts in the meetings that led to the development of the manuscript. All authors actively contributed to the discussion and the consensus reached and drafted part of the manuscript. Bassem Yamout and Maya Zeineddine drafted the initial version of the manuscript and all authors discussed and reviewed the final version of the manuscript. All authors read and approved the final submitted manuscript, and agreed to be accountable for the work.

Ethics approval: Not Applicable

Consent to participate: Not Applicable

Consent for publication: Not Applicable

Availability of data and material: Not Applicable

Code availability: Not Applicable

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Table 1. NMOSD Criteria in Current Use

2015 International Panel for NMO Diagnosis (IPND) criteria*	
Diagnostic criteria for anti-AQP4(+) NMOSD 1. At least 1 core clinical characteristic 2. Positive test for AQP4-IgG 3. Exclusion of alternative diagnoses	**Diagnostic criteria for NMOSD without AQP4-IgG and NMOSD with unknown AQP4-IgG status** 1. At least 2 core clinical characteristics a. At least 1 core clinical characteristic must be ON, acute myelitis with LETM, or APS b. Dissemination in space (≥ 2 different core clinical characteristics) c. Fulfillment of additional MRI requirements, as applicable 2. Negative test for AQP4-IgG using best available method[a] 3. Exclusion of alternative diagnoses
Core clinical characteristics 1. ON 2. Acute myelitis 3. APS: episode of otherwise unexplained hiccups or nausea and vomiting 4. Acute brainstem syndrome 5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions 6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions	**Additional MRI requirements for NMOSD without AQP4-IgG and NMOSD with unknown AQP4-IgG status** 1. Acute ON: requires brain MRI showing a) normal findings or only nonspecific white matter lesions, or b) optic nerve MRI with T2 or gad(+) lesion extending over >1/2 optic nerve length or involving the optic chiasm 2. Acute myelitis: requires associated intramedullary MRI lesion extending over ≥ 3 contiguous segments (LETM) or ≥ 3 contiguous segments of spinal cord atrophy 3. APS: requires associated dorsal medulla/area postrema lesions 4. Acute brainstem syndrome: requires associated periependymal brainstem lesions

[a] Or testing unavailable.

Abberviations: *AQP4 = Aquaporin-4; APS = Area Postrema Syndrome; IgG = Immunoglobulin G; Gad(+) = Gadolinium-enhancing; LETM = Longitudinally extensive transverse myelitis; MRI = Magnetic resonance imaging; NMO = Neuromyelitis optica; NMOSD = Neuromyelitis optica spectrum disorder; ON =optic neuritis; CBA = Cell-based assays*

Table 2. Comparative Clinical, Imaging, and Laboratory Features of NMOSD, MS, MOGAD, and ADEM

	NMOSD	MS	MOGAD	ADEM
Epidemiology	• High female predominance (F/M ratio 9:1) • Mean age of onset 25-35 years	• Moderate female predominance(F/M ratio 3:1) • Mean age of onset 40-45 years	• No female predominance(F/M ratio (1:1) • Age at onset: 0-40 years, more common in childhood	• Age of onset: predominantly affects children
Clinical Features	• NMOSD relapses are usually severe, often involving optic nerves and area postrema, with incomplete recovery • The course is mainly relapsing without evidence of progression	• Progressive disability at different stages of the disease.	• Relapsing or monophasic course (50%) • Better prognosis and higher likelihood of recovery from relapses than NMOSD**.**	• Typically, monophasic • Presence of encephalopathy • No new symptoms, signs or MRI lesions after three months of initial ADEM
MRI Imaging	• Longitudinally extensive transverse myelitis • Optic nerve lesions extending more than half the optic nerve or involving the optic chiasm • Dorsal medulla lesions • Periependymal lesions • Large confluent hemispheric lesions • Central spinal cord lesions • Spinal cord bright spotty lesions	• Multifocal brain lesions, often located in periventricular, juxtacortical, and infratentorial regions • MRI characteristics that suggest MS include periventricular lesions in the inferior temporal lobe, cortical/juxtacortical lesions, and Dawson's fingers • Peripheral spinal cord lesions	• Longitudinally extensive transverse myelitis • Conus medullaris lesions • Bilateral optic neuritis is more common in MOGAD compared to NMOSD (63 vs 25%) • Perineural optic nerve enhancement • ADEM-like fluffy lesions • Leptomeningeal enhancement • Resolution of lesions is more common in MOGAD	• Confluent large fluffy white matter lesions • Internal capsule and thalamic lesions • T1 hypointense white matter lesions are rare
CSF Analysis	• Oligoclonal bands are infrequently seen in NMOSD (20-30%) • Pleocytosis, occurs in about	• Oligoclonal bands are commonly found in the CSF (90-95%)	• Oligoclonal bands are rarely found in CSF (10-20%) • Pleocytosis, occurs in about 35% of cases	• Oligoclonal bands are found in less than 10% and may be transitory • CSF pleocytosis is observed in a wide

	35% of cases, with a predominance of neutrophils or eosinophils			range of patients (28–86%)
Serology	• Serum AQP4 antibodies are highly specific for NMOSD		• High titers anti-MOG antibodies (>1:100) are strongly suggestive of MOGAD	

Abbreviations: ADEM= Acute Disseminated Encephalomyelitis ; AQP4= Aquaporin-4; CSF= Cerebrospinal Fluid ; F/M= Female to Male ; NMOSD= Neuromyelitis Optica Spectrum Disorder; MOGAD= Myelin Oligodendrocyte Glycoprotein Antibody Disease ; MRI= Magnetic Resonance Imaging ; MS= Multiple Sclerosis